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Bisphosphonate-related osteonecrosis of the jaws: Report of two cases with breast cancer, a dental concern and review of the literature

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Abstract

Bisphosphonates are becoming increasingly important in the treatment of metabolic and oncological diseases involving the skeleton. In recent years, several cases of necrosis of the jaws associated with long-term use of bisphoshponates have been reported. The management of bisphosphonate-related osteonecrosis of the jaws (BRONJ) is emerging as a significant problem in the field of dentistry. In this article, we report two new cases of patients with osteonecrosis induced by bisphosphonates. Two unrelated female patients undergoing treatment with bisphosphonates for metastatic breast cancer were referred to the department of oral surgery due to non-healing extraction sockets and intraoral exposed bone after dental extraction. The treatment modality of case 1 included antibiotic therapy, sequestrectomy, periodontal flap, and chlorhexidine mouthwashes. After an eleven-month follow-up period the affected area has healed totally. The other patient refused any surgical intervention. In addition, this article reviews the current literature describing the dental procedures for patients with BRONJ.

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Introduction

Breast cancer has high incidence and is a common cause of cancer-related death in women worldwide. The most common site of distant metastasis in breast cancer patients is the skeleton [1]. Bone metastasis are a common occurrence in advanced cancer and can be responsible for several morbidity outcomes including pathological fractures, pain, impaired mobility, hypercalcemia, bone marrow infiltration and spinal cord compression [2]. Bisphosphonates (BPs) are enormously effective in reducing the symptoms and complications in many skeletal disorders [3]. BPs, such as pamidronate or zoledronic acid, are commonly used for the prevention and treatment of pathological fractures in patients with breast cancer [4]. Therefore, educating dentists and physicians who treat maxillofacial diseases about bisphosphonate-associated side effects, especially BRONJ, is important [5].

Osteonecrosis of the jaw is characterized by bone death as a consequence of a wide variety of systemic and local factors that compromise bone blood flow [6]. The main cause of bone necrosis is a defect in vascularization. The appearance of BRONJ is very similar to the one of osteonecrosis associated with environmental pollutants, pre-existing diseases, radiotherapy, chemotherapy, as well as many popular medications [7]. Recently, BRONJ has been included in the summary of product characteristics [8].

Bisphosphonate-associated osteonecrosis of the jaw (BONJ) is a concerning side effect of bisphosphonates. Bisphosphonates play an important role in the therapy of breast cancer patients with osseous metastases. Depending on the ligands, bisphosphonates are separated into nitrogen-containing and non-nitrogen-containing bisphosphonates. The former inhibit the mevalonate pathway, and the latter are integrated into the ATP molecule. Both mechanisms result in a cytotoxic effect on the osteoclasts. There is further evidence that bisphosphonates reduce and delay skeletal-related events and reduce pain and thereby improve quality of life [8].

In 2003, after alert initial observations by Marx [9], Rosenberg [10] and Migliorati [11] reported unusual findings of osteomyelitis-like lesions which associated the use of bisphosphonates with the appearance of exposed bone of the jaws in the oral cavity and the development of osteonecrosis; the authors called this condition BRONJ. Although bisphosphonates have been in clinical use for several years, an increasing number of articles on these drugs relating them to osteonecrosis [12-14] in patients with breast, lung or prostate cancer or multiple myeloma, have been reported, usually, but not always, in those who have undergone head and neck radiotherapy or a dental procedure [15].

According to the American Association of Oral and Maxillofacial Surgeons [16], it was established that three characteristics must be present to diagnose a BRONJ: (a) previous or current medical treatment with a bisphosphonate; (b) exposed necrotic bone in the maxillofacial region that has persisted for more than eight weeks; and (c) no history of radiation therapy of the jaws. The mandible is more commonly affected than the maxilla (2:1 ratio) [2]. The main risk factor for this complication is a previous history of dento-alveolar surgery, periodontal diseases with odontososis, or denture pressure sores; the remaining cases occur spontaneously [12,17].

The literature suggests BRONJ incidence rate of 0.028% to 4.3% [18]. Only a few studies have been published about BRONJ in breast cancer patients [8, 19-21]. The real prevalence of bisphosphonate-associated osteonecrosis of the jaw in breast cancer patients is unknown due to the fact that most cases are spontaneous reports, or results of retrospective analyses; an incidence rate of 2.5% [18] , 2.9% [19], 5.3% [8] and 11.4% [21] has been reported. Patients taking oral bisphosphonates have significantly lower risk of developing BRONJ than those treated with IV bisphosphonates. The risk of BRONJ in patients receiving oral bisphosphonates may be related with continuous therapy for more than three years [12].

The appearance of bisphosphonate-associated osteonecrosis is identical to the appearance of osteoradionecrosis in patients who develop it after undergoing head and neck irradiation [9]. Patients who are at risk of BRONJ or those with established BRONJ may also present with other common clinical conditions which must not be confused with BRONJ. The differential diagnosis of BRONJ contains, but is not limited to: alveolar osteitis (dry socket), sinusitis, gingivitis, periodontitis, caries, periapical pathology, lingual bony sequestrum, and temporomandibular disorders. Some of these conditions, such as periodontitis and periapical pathology, could also contribute to the development of BRONJ in patients at risk [16].

Similar to osteoradionecrosis, the radiographic features of BRONJ have many similarities to that of chronic osteomyelitis [22]. Various skeletal radiographic features associated with BRONJ in conventional periapical and panoramic radiographs, computed tomography, magnetic resonance imaging, and nuclear bone scanning have been described [23]. Clinical presentations generally are almost unnoticeable or slight at the start, but with time they become severe causing mucosal dehiscence, non-healing mucosal ulcers, extensive bone sequestrums, suppuration, and mucosa or cutaneous fistula with continuous and intense pain [24]. Radiographs of the jaw reveal areas of sclerosis, destruction, sequestration, or pathologic fractures. Delayed or persistent tooth sockets after extraction may also be revealed in these patients [25].

Treatment of BRONJ is difficult and depending on the stage of the disease. Therapy ranges from simple mouth rinses for asymptomatic exposed bone to debridement and huge resections of the maxilla or the mandible, the latter having a large impact on the quality of life for these patients [26].

It is important to realize that BRONJ is a new clinical entity, and new cases are being reported daily. We report two cases of patients with osteonecrosis of the jaw associated with bisphosphonate therapy. We discuss management options, as well as recent guidelines for treatment.

Case Reports

Case 1

A 61 year-old woman was referred to our clinic in November 2009 to evaluate "an infection at the left premolar-molar area of the mandible and left canine area of the maxilla after a dental extraction that, after four months, had not responded to treatment with antibiotics". In discussing her medical history the patient pointed out that she had been diagnosed with breast cancer in 2006 and had been treated with chemotherapy. She had been receiving bisphosphonate therapy for four years, and then she was receiving zoledronic acid at the time of the extractions. She also had a history of vertebrate fractures, and zoledronic acid intravenous administration in doses of 4 mg during the previous 3 years.

The patient reported the presence of non-healing extraction sites after undergoing the extraction of an

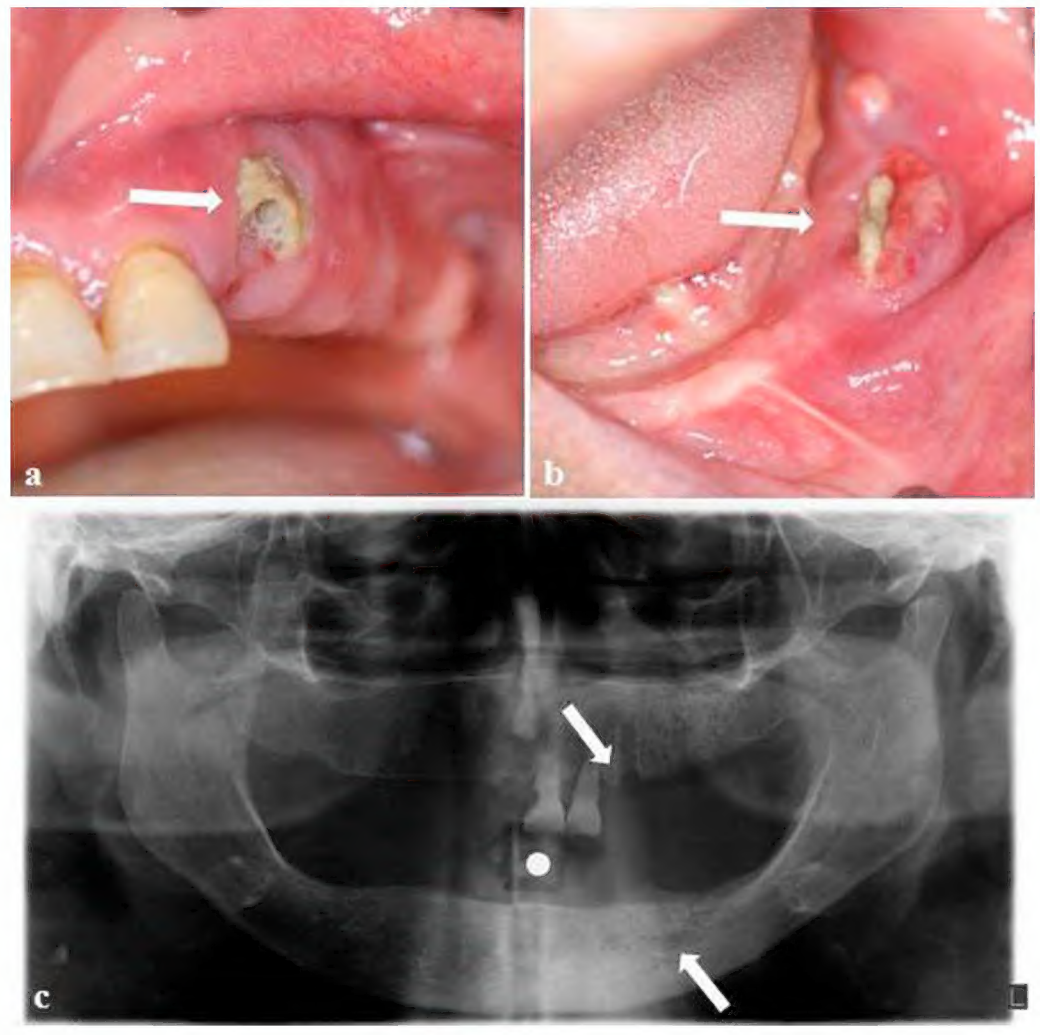

Figure 1. Clinical photographs and radiographic image from Case Report 1. **(a,b)** Clinical photograph of the non-healing extraction sites of maxillar left canine (a) and mandibular left premolar-molar area four months after their removal showing necrosis of the alveolar bone and surrounding tissue; **(c)** Radiographic view of the osteonecrosis around the extraction sites of teeth nos 11, 19 and 20 in a female patient with breast cancer undergoing treatment with pamidronate and zoledronate.

unrestorable tooth, no. 11, by her general dentist five months before her initial visit to us. In addition, teeth nos. 19 and 20 had extreme mobility because of periodontal problems and were extracted. Her general dentist carried out these procedures without flap reflection or primary closure. Three months after the extraction of the teeth, her dentist observed that the patient had delayed healing of all three extraction sites and exhibited exposed necrotic bone in the extraction sites in spite of antibiotic therapy. The patient was re-examined a month later, with no improvement in her condition. In addition, she reported that she had not disclosed her bisphosphonate use to either her general dentist or previous oral surgeon until after the extractions had been performed as she did not think this medication was relevant to her current dental condition or treatment.

In intraoral exploration non-healing extraction sockets were found and the surrounding alveolar bone was partially exposed. The associated mucosa appeared red and inflamed. Purulent exudate (Figure 1 a, b) and an extraoral fistula were also present (Figure 1 c). BRONJ was diagnosed by a maxillofacial surgeon based on the following criteria: exposed bone in the maxilla or mandible associated with pain and soft-tissue swelling, unhealed necrotic bone after dental work, long-term use of bisphosphonates, not having received radiation therapy, and poorly demarcated radio-opaque area of the affected bone on X-ray. However, under a local anesthetic the minimum debridement of a necrotic bone was performed; a biopsy was taken, and a microbiological culture was made. From the results, diagnosis of BRONJ was confirmed.

The differential diagnosis of the lesion included a fungal infection secondary to her immunocompromised status, as well as osteoradionecrosis. The oral surgeon ruled out the latter because the patient reported that she had not received radiation therapy.

After consulting with the patient's oncologist, treatment with intravenous zoledronic acid was discontinued. After the discontinuation of bisphosphonate therapy, we instructed the patient to use a 0.12% chlorhexidine oral rinse three times a day and initiated therapy with an antibiotic (amoxicillin-clavulanic acid 1g twice daily) by oral administration and non-steroid anti-inflammatories. Ten days later, the patient revisited our department as requested. Under local anesthesia and antibiotic coverage, an oral surgeon explored the patient's extraction sites and debrided, and excised the diseased and necrotic osseous, and soft tissues. He removed necrotic alveolar bone until reaching what appeared to be bleeding vital osseous tissue. He removed necrotic alveolar bone until reaching what appeared to be bleeding vital osseous tissue. He irrigated the site close to the operative site and instructed the patient to use a chlorhexidine oral rinse three times a day and initiated long-term antibiotic therapy with 500 mg of penicillin VK twice a day. At the three-week postoperative visit, the subject had no complaints. Healing in the affected area was progressing well and no bleeding or purulent exudate were present.

The subject failed to report for her five-month check-up. At the five-month postoperative visit (in May 2010),

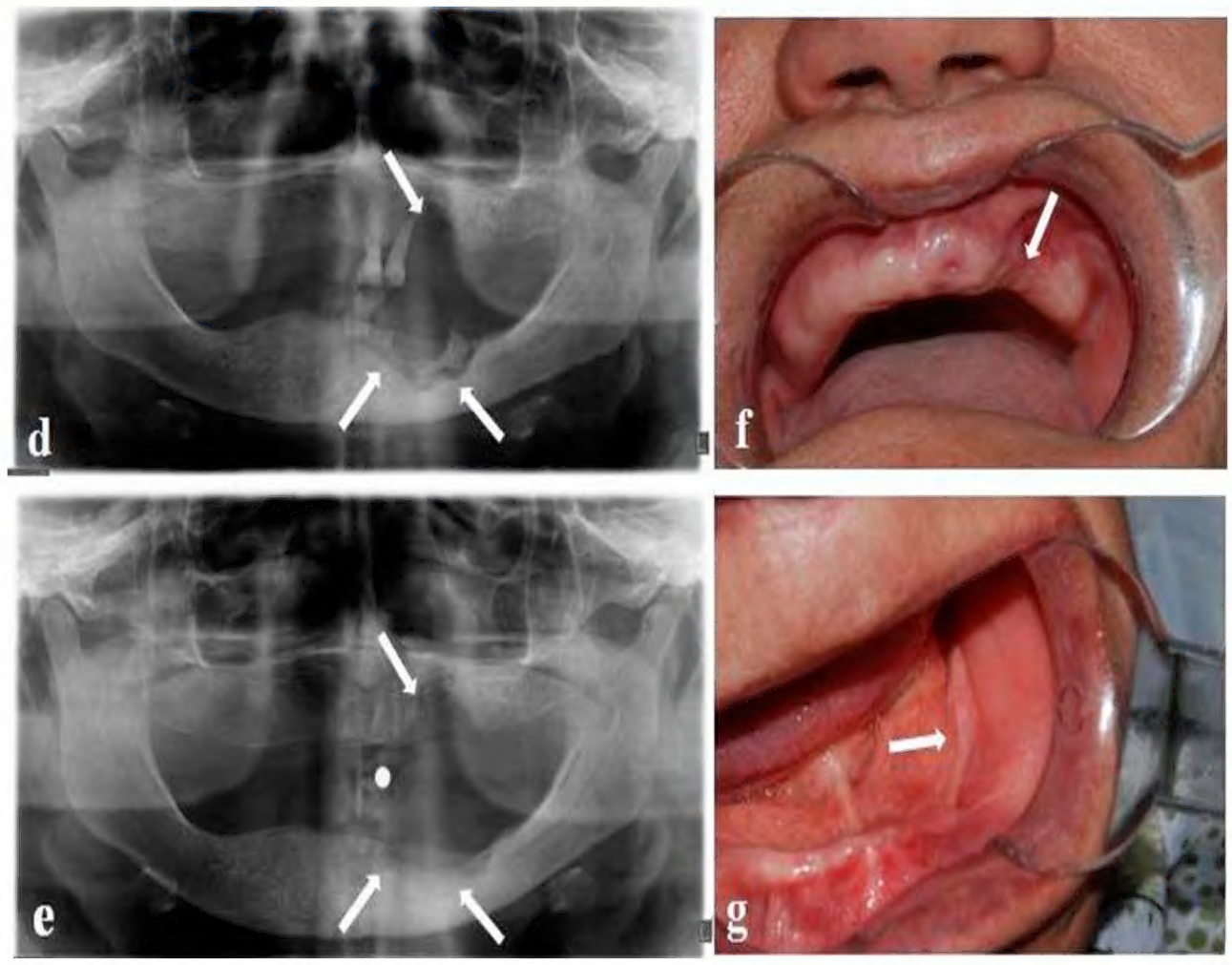

Figure 1. Clinical photographs and radiographic images from Case Report 1. **(d)** Panoramic radiograph taken at second visit confirmed the progression of the osteonecrosis to fracture in five weeks. Note the sequestrum in the left mandible; **(e)** The panoramic radiograph taken 11 months after the patient's first visit to our department showing the standardized area; **(f,g)** Photographs of the patients' jaws showing two examples each of upper and lower jaw complete response to therapy.

the patient had evolved towards a clinical and radiographic improvement, and the pain had diminished almost completely although the soft tissue around the sockets had not healed. Purulent exudate was observed and a great bone area of sequestrum was delimited in the extraction areas (Figure 1d).

An oral surgeon performed the previous treatment procedures. He also extracted teeth nos. 9 and 10. He irrigated the site, undermined the flap margins to gain tension-free flap closure and closed the operative site with multiple interrupted polypropylene sutures. We instructed the patient to use a chlorhexidine oral rinse three times a day and initiated antibiotic therapy as previously explained.

The patient returned to our department two weeks later for a follow-up check. The oral examination revealed evidence of soft-tissue breakdown of the flap closure, with visible necrotic alveolar bone in the region of tooth no.11. Purulent exudate was observed. The oral surgeon debrided the site again, under local anaesthesia and antibiotic coverage, until he observed viable bleeding bone. He irrigated the site and closed the operative site. The oral surgeon instructed the patient to use a chlorhexidine oral rinse three times a day and initiated antibiotic treatment (amoxicillin-clavulanic acid 1g twice daily plus metronidazole 1 g daily). At the three-week postoperative visit, the subject had no complaints. Healing in the affected area was progressing well and no bleeding or purulent exudate were present.

We followed up the patient every month to reevaluate the affected areas and to ensure that they had not become suppurative. The patient was treated with antibiotics until the areas healed. The outcome, although slow and torpid, has been a significant improvement, and at this moment, 11 months after the initial diagnosis, our patient is asymptomatic and has no evidence of infection. There was a complete mucosal coverage. In the panoramic X-ray, the image has been standardized (Figure 1 e) and we can see that the intraoral soft tissue has completely healed (Figure 1 f, g). The patient is being followed up in scheduled check-ups.

Case 2

A 49-year-old female patient was referred to the Department of Oral Diagnosis and Radiology at the Faculty of Dentistry with chief complaints of pain in the left mandible. The patient reported the presence of non-healing extraction sites after undergoing the extraction of unrestorable teeth nos. 18 and 19 by her dentist two years prior her initial visit to us. Her dentist carried out the procedures without flap reflection or primary closure. Four months after the extraction of the teeth her dentist noted that the patient had a delayed healing of the extraction sites and exhibited exposed necrotic bone in them. The patient was re-examined five weeks later and no improvement was observed in her condition in spite of antibiotic therapy.

In discussing her medical history she pointed out that she had been diagnosed with metastatic breast cancer (MBC) and had been treated with the intravenous (IV) bisphosphonate drug zoledronate prescribed by her oncologist. She had been taking 4 milligrams monthly for

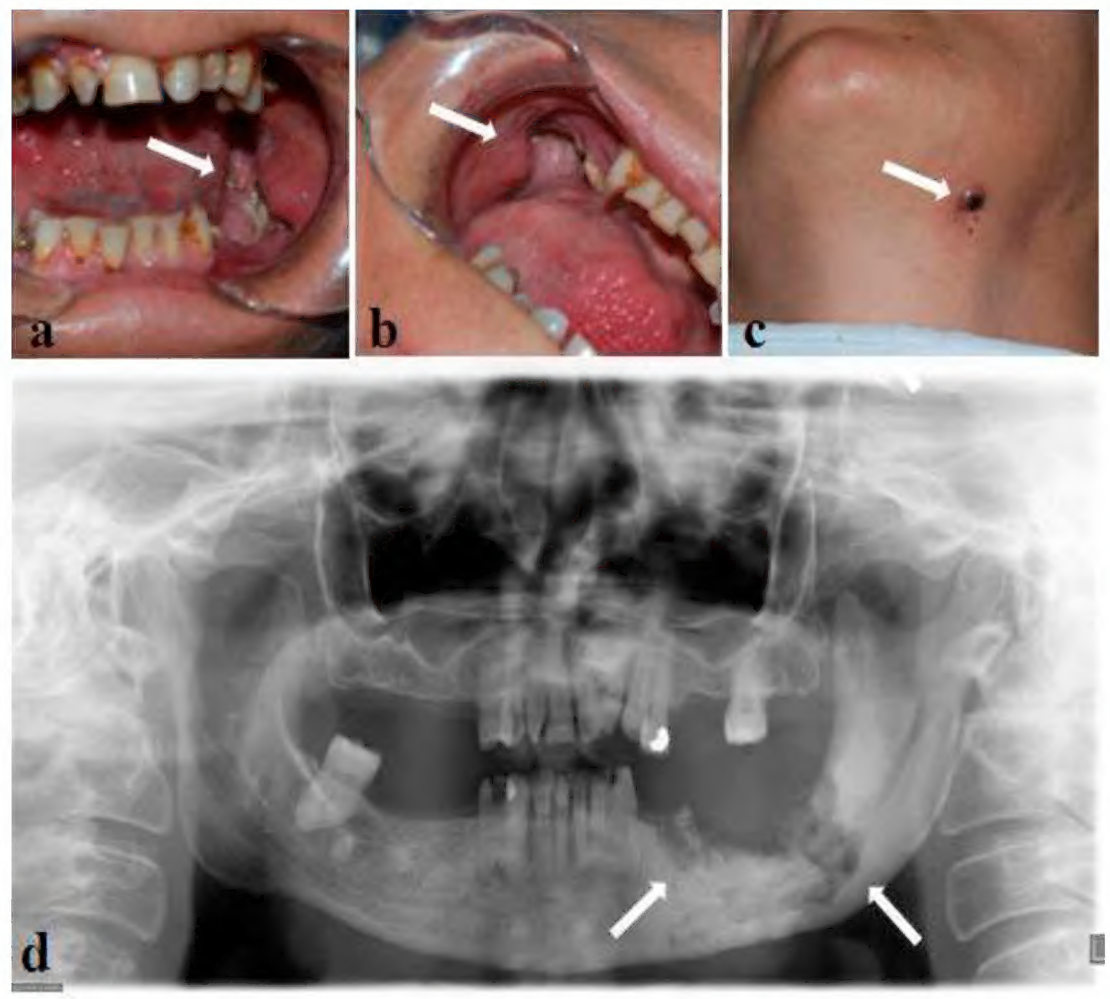

Figure 2. Clinical photographs and radiographic image from Case Report 2 **(a,b)** Intraoral examination of the patient with metastatic breast cancer who used pamidronate and zoledronic acid for at least four years revealed an extensive area of osteonecrosis; **(c)** The left mandible had a large area of osteonecrosis that became secondarily infected, leading to the formation of an extraoral fistula; **(d)** Panoramic radiograph of patient showing a body defect with ill-defined margins and multiple irregular radiopacities interspersed within the lesion, indicating multiple sequestra

the treatment of her MBC. At that point she had been receiving bisphosphonate therapy for five years since being diagnosed with breast cancer. In addition to MBC, which was diagnosed two years before she came to our department, the patient also had, according to her medical history, hypertension, asthma and diabetes. She was on zoledronic acid at the time of the dental extractions. In addition, she reported that she had not disclosed her bisphosphonate use to either her general dentist or previous oral surgeon until after the extractions had been performed as she did not think this medication was relevant to her current dental condition or treatment.

In oral examination, there was a significant bony depression and the surrounding alveolar bone was partially exposed (Figure 2 a, b). The associated mucosa appeared red and inflamed. Purulent exudate was also present. The left mandible had a large area of osteonecrosis that became secondarily infected, leading to the formation of an extraoral fistula (Figure 2 c). A panoramic radiograph taken at the subject's visit showed a deep bony defect in the left premolar- molar area (Figure 2 d).

BRONJ was diagnosed by a maxillofacial surgeon based on the same criteria as in case 1. We recommended that she undergo treatment consisting of antibiotics and surgical debridement. The oral surgeon irrigated the site. Although we considered removing bisphosphonate therapy from the patient's chemotherapy regimen, the patient's oncologist and other members of the medical team did not advise doing so owing to the profound beneficial effects that these drugs were having on the patient's quality of life. We instructed the patient to use a 0.12% chlorhexidine oral rinse three times a day and initiated therapy with an antibiotic (amoxicillin-clavulanic acid 1g twice daily plus metronidazole 1 g daily) by oral administration and non-steroid anti-inflammatories. In the following three weeks, the pain diminished almost completely. The oral surgeon recommended the patient to have surgical intervention to resect the left mandibular body from the angle to the canine region and to insert a titanium reconstruction bar. However, the patient refused any surgical intervention but continued to be followed up. Unfortunately, shortly after her last visit to our department, the patient died of metastatic breast carcinoma.

Discussion

Bisphosphonates are important drugs that are used widely for several medical purposes including the prevention and treatment of bone metastases associated with cancer [27-31]. They are enormously effective in reducing the symptoms and complications in many skeletal disorders such as bone metastases, osteoporosis, Paget's disease, hypercalcemia of malignancy and bone pain [5, 32]. While bisphosphonates have not been shown to improve cancer-specific survival, they have had a significant positive effect on the quality of life for patients with advanced cancer involving the skeleton [16]. Although the exact disease mechanism for bone necrosis related to bisphosphonate therapy has not been established, these drugs are understood to hinder the

resorption of bone by the inhibition of osteoclastic activity.

Although causality may never be proven, emerging experimental and epidemiologic studies have established a strong association between bisphosphonate treatment and the appearance of painful exposed nonvital bone in the jaws after oral surgery has been reported in the last decade [33]. There is evidence that patients with an additional risk factor for osteonecrosis, such as radiation of the head and neck area, have an increased risk of developing BRONJ [34]. Various potential risk factors for the development of osteonecrosis of the jaws may include: use of bisphosphonates such as pamidronate, zoledronic acid and alendronate, concomitant therapy with steroids, dental extraction, dental implant placement, periodontal disease, periapical surgery, periodontal surgery involving osseous injury, surgical bone manipulation, presence of oral infection, infectious disease, and/or trauma, head and neck radiotherapy, chemotherapy, immunotherapy, demographic and systemic factors (multiple myeloma, cancer metastatic to the bone such as breast, lung and prostate, renal dialysis, low haemoglobin, obesity, diabetes) [35], other cancer treatment protocols, coagulopathies, genetic factors [36], bone exostosis, previous invasive dental procedures, dental prostheses, vascular disorders, advanced patient age (older than 65 years) [37], alcohol abuse and malnutrition [11,38,39].

Bisphosphonates (BPs) are divided into two types depending on administration method - intravenous infusion and oral administration. Patients taking oral BPs manifested less bone exposure and milder symptoms compared to patients on IV BPs [18]. It has been reported that oral BPs posed a lower risk since it took longer to develop bisphosphonate-induced osteonecrosis because of a slower accumulation rate in the bone [22]. Pamidronate is 10 times more potent than clodronate, while zoledronate is 10,000 times more potent in its osteoclastic inhibitory activity than the oral bisphosphonate [40]. However, there are many patients taking oral BPs for the treatment of osteoporosis, so it is very important to assess the risks, especially in patients taking BPs for a long period of time (longer than 3 years) [12].

Recently, cases of BRONJ in patients with various types of cancer receiving intravenous bisphosphonates, such as pamidronate and zoledronic acid to control and treat metastatic bone disease, have been reported in the medical and dental literature of [9, 11, 22, 39]. In addition, researchers have reported several cases of BRONJ in patients taking oral doses of alendronate to treat osteoporosis or osteopenia [39].

Usually patients with BRONJ are asymptomatic in the initial stage but with time severe symptoms appear causing extensive bone sequestrums, suppuration, and mucosa or cutaneous fistula with continuous and intense pain [22, 41].These lesions typically become symptomatic following a secondary infection or trauma to adjacent and/or opposing healthy soft tissues from irregular surfaces of the exposed bone [42]. Absent or delayed hard- and soft-tissue healing after dental operations such as prior tooth extraction, surgical dental procedures, periodontal diseases with odontososis, or denture pressure sores are the most common clinical history associated with BRONJ [9,22,39].

When tissues are severely infected, patients may complain of acute pain and lack of sensory sensation (paresthesia). This may be an indication of peripheral nerve compression [39]. In patients who develop BRONJ spontaneously, the most common initial grievance is the sudden presence of intraoral discomfort and the occurrence of roughness that may progress to traumatize the oral soft tissues encircling the area of necrotic bone. Therefore the diagnosis of BRONJ is based on the medical and dental history of each patient, as well as the observation of clinical signs and symptoms of this pathological process [39].

Radiographic findings vary from no evidence of bone changes to bone sclerosis, lytic areas and obvious sequestration [12, 22]. BRONJ is similar in clinical appearance to osteoradionecrosis (ORN), where the lesions develop after radiotherapy to the head and neck area, typically for the management of malignant tumours [59].

In the early stages of BRONJ no significant changes may appear on radiographs. Later, radiographic changes may mimic classic periapical inflammatory lesions or osteomyelitis. Other radiographic findings include non-healing extraction site, widening of the periodontal ligament space and osteosclerotic lamina dura [15, 56]. In cases of extensive bone involvement areas of mottled bone similar to that of diffuse osteomyelitis become evident. Radiological and nuclear medical imaging can be of crucial value in helping the recognition and definition of bone lesions in patients on therapy with bisphosphonates [44]. Involvement of the inferior alveolar canal can be associated with paresthesia of the lower lip [39]. In the second case in this report, paresthesia of the dental nerve on the left side of the mandible progressed to profound anesthesia and we found radiographic evidence of osteolysis into the inferior alveolar canal.

Procedures for the treatment strategies of patients using these drugs have been outlined by task forces from the American Dental Association [45], the American Association of Oral and Maxillofacial Surgeons [16], the American Society for Bone and Mineral Research [46], and the American Academy of Oral Medicine [39]. Currently, the results for the treatment and long-term assessment of management and prevention programs from these task forces have not been determined. Consequently, many of the suggestions for patient

management have been dependent on authority opinions [6].

The staging system and treatment strategies have been proposed by these institutions (Table 1). In our first case, the patient was in stage 2 and this treatment plan (local debridement, sequestrectomy, use of antibiotics, daily chlorhexidine mouth rinsing) was performed successfully. Several different adjunctive treatments (ie, hyperbaric oxygen [47, 48], parathyroid hormone [49], platelet-rich plasma [50], laser [51, 52], ozone therapy [53]) have been advocated to improve healing in BRONJ, but their benefits remain to be clarified.

BRONJ is a recently documented oral complication, and proven effective therapeutic measures have not yet been identified. The management of patients receiving oral or IV bisphosphonate therapy is mainly preventive in nature [39]. Based on the possible correlation between jaw osteonecrosis and bisphosphonates, before and during bisphosphonates therapy, all patients who are going to begin treatment with bisphosphonates should have a comprehensive dental clinical examination, and an appropriate radiographic study [16, 39, 45]. All patients should be educated prior to starting therapy about this possible complication and instructed to avoid elective invasive dental procedures that may not heal completely. They should also be given information about BRONJ and be made aware of the early symptoms of development of this condition [40].

Management of dental care for patients receiving bisphosphonate therapy should be directed at reducing the future need for dentoalveolar surgery [16, 39, 45]. Before initiation of the bisphosphonate treatment it is essential to evaluate the patient's oral physical condition in terms of high-quality oral hygiene and plaque control, and appropriate periodontal, restorative, endodontic and surgical treatments in order to prevent any probable cause of infection which may reach the bone, and to avoid invasive oral interventions in the near and intermediate future [54]. Any unsalvageable teeth should be removed, all invasive dental procedures should be completed and optimal periodontal health should be as atraumatic as possible, with gentle soft-tissue management. When invasive dental events are to be performed electively, some researchers have recommended withholding intravenous bisphosphonates for one to three months before the process and resuming treatments only after oral healing is complete [55].

There has been much discussion as to the benefits of stopping the drug for a period of time, a so called 'drug holiday'. It is suggested that cessation of BP treatment allows for regeneration of osteoclasts and therefore improved bone turnover, and this has some support from studies looking at biochemical markers of bone turnover, but there is no consensus on the duration of drug holiday necessary for this to occur. Any decision on temporary cessation of BP therapy must obviously be taken in conjunction with the prescribing physician and whether this is possible will be determined by the clinical indication for BP therapy [56].

Shannon et al. stated that it is uncertain whether stopping bisphosphonate therapy will help manage BRONJ once the drug has been incorporated into bone. Because the half-lives of most bisphosphonates are months to years, there is no strong evidence that

Table 1. Staging and treatment strategies

BRONJ	Clinical condition	Treatment Strategies
Risk stage	No evidence of necrotic bone in asymptomatic patients who have been treated with IV or oral bisphosphonates.	No treatment indicated, patient education
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms.	Systemic administration, including the use of pain medication and antibiotics.
Stage 1	Asymptomatic exposed necrotic bone without soft tissue infection.	Antimicrobial mouthwashes (ie, chlorhexidine 0.12%, hydrogen peroxide), no surgical treatment is indicated, clinical follow-up.
Stage 2	Presence of symptoms around the area of necrotic and exposed bone associated with pain, soft tissue inflammatory swelling or secondary infection.	Antimicrobial rinses (ie, chlorhexidine 0.12%), systemic antibiotics or antifungals (infections may exacerbate BRONJ), pain control, and superficial debridement to relieve soft tissue irritation.
Stage 3	Presence of a pathological fracture (not related to metastatic disease), necrotic and exposed bone with associated infection, pain, and at least one of the following: pathologic fracture, extraoral fistula, oral antral/oral nasal communication osteolysis extending to the inferior border of mandible.	This stage of necrosis usually requires surgical debridement/resection to reduce the volume of necrotic bone in addition to conservative measures of analgesics, culture directed oral/intravenous antibiotics and oral antimicrobial rinses (ie, chlorhexidine 0.12%).

discontinuation of treatment before dental procedures will significantly affect the occurrence of BRONJ, but some suggest that, if the person has already undergone oral bisphosphonate therapy for longer than three years, or for less than three years while taking corticosteroids, the bisphosphonate treatment should be stopped at least three months before a surgical procedure and, if possible, not resumed until osseous healing occurs because the combination of the two drugs may increase the risk of BRONJ. Particular care should be taken with people taking IV bisphosphonates, who should be advised to avoid elective invasive dental procedure during therapy; if the person develops BRONJ, dental surgery may exacerbate the condition. Careful consultation between the dentist, physician, and patient is necessary before any modification or cessation of treatment is considered [57].

Although interrupting or reducing bisphosphonate exposure might have beneficial effects on the development of BRONJ, it is unlikely that bisphosphonate discontinuation for a short period of time will allow significant reduction in the risk of developing BRONJ. As a result, it is not clear how long bisphosphonate interruption or reduction is required to achieve significant decrease in the risk of development of BRONJ [58].

Some authorities reported that preventative dental management reduced the risk of BRONJ among patients with malignancy treated with IV bisphosphonates. These results proposed that, althoughthe risk of BRONJ is not eliminated, dental evaluations and treatment prior to initiating IV bisphosphonate therapy among cancer patients decreases the risk of the condition [59]. Patients without BRONJ but who are already taking bisphosphonates should be referred to a dentist or oral maxillofacial surgeon for a careful examination.

In conclusion, bisphosphonates are the drugs of choice for many life-threatening diseases. It is important that health professionals, especially dentists, oncologists and oral surgeons be aware of the association between bisphosphonate treatment and delayed wound healing and osteonecrosis of the jaws. They should perform a comprehensive oral examination in patients before they begin any chemotherapy regimen. They should also follow existing guidelines for dental consultation for the prevention of oral complications of cancer therapy. Patients should be educated by specialists about the possible dental side effects of bisphosphonate therapy and take the necessary preventive measures to keep potential side effects to a minimum.

In addition, continued high-quality clinical research on the prevention, risk reduction, and treatment of BRONJ needs to be developed further so that more precise decisions regarding risk, prognosis, proper dental management option, and results can be established for patients with BRONJ.

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